REMARKS/ARGUMENTS

The amendments to the specification and claims are fully supported by the specification and claims as originally filed and do not constitute new matter.

Prior to the present amendment, Claims 28-40 were pending in this application and were rejected on various grounds. With this amendment, Claim 37 has been canceled without prejudice. The rejection of the remaining claims is respectfully traversed.

Claims 28-36 and 38-40 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

Priority Determination

The Examiner asserts that the effective filing date for the application is December 6, 2001, the actual filing date of the instant application, and that Applicants are not entitled to claim priority to earlier-filed applications because "none of the parent applications provide a specific and substantial asserted utility or a well established utility for the claimed invention." See page 2, of the instant Office Action.

As discussed below, Applicants rely on the gene amplification assay (Example 143) for patentable utility which was first disclosed in U.S. Provisional Application No. 60/162,506, filed October 29, 1999, priority to which has been claimed in this application.

As will be shown, the disclosure of the instant application, which is similar to that of the earlier-filed application (see Example 20, Provisional Application No. 60/162,506), provides the support required to establish utility for the claimed protein, for example, in detecting over-expression or absence of expression of the PRO1293 polypeptide. Accordingly, Applicants submit that the subject matter of the instant claims is supported by the disclosure in U.S. Provisional Application No. 60/162,506. Therefore, the effective filing date of this application is October 29, 1999, the filing date of U.S. Provisional Application No. 60/162,506.

Information Disclosure Statement

The Examiner notes that the information disclosure statements filed on August 27, 2002 and November 5, 2002 do not give sufficient identifying information because they do not identify each reference by author and publication date. In response, Applicants file herewith, an Information Disclosure Statement listing each reference separately and including authors/inventors, relevant accession numbers and publication dates. Applicants respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application.

Specification

The specification has been amended to remove embedded hyperlink and/or other form of browser-executable code. The specification has been amended to remove embedded hyperlink and/or other form of browser-executable code. Further, the paragraph beginning at page 513, line 13, has been amended to comply with the provisions of the Budapest Treaty.

Claim Rejections Under 35 U.S.C. §101

Claims 28-40 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

The Examiner specifically notes that "the specification does not disclose any information regarding physiologic activity or functional characteristics of the PRO1293 polypeptide." The Examiner also alleges that the "specification does not demonstrate that the PRO1293 polypeptide is actually overly expressed in any of the cancers mentioned" and that "Applicants have not shown that there is a relationship between protein expression and the over-expression of the gene." See page 4, of the instant Office Action. Therefore, the Examiner concludes that the PRO1293 polypeptide lacks specific and substantial asserted utility or a well established utility.

Applicants respectfully disagree and traverse the rejection.

Applicants submit that the cancellation of Claim 37 renders the rejection of this claim moot.

First of all, gene amplification is an essential mechanism for oncogene activation. The gene amplification assay is well-described in Example 143 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 8, including primary lung and colon tumors of the type and stage indicated in Table 7. As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control. Gene amplification was monitored using real-time quantitative TaqMan PCR. Table 8 shows the resulting gene amplification data. Further, Example 143 explains that the results of TaqMan™ PCR are reported in ΔCt units, wherein one unit corresponds to one PCR cycle or approximately a 2-fold amplification relative to control, two units correspond to 4-fold amplification, 3 units to 8-fold amplification etc.

Applicants respectfully submit that ΔCt value of at least 1.0 was observed for PRO1293 in at least three of the tumors listed in Table 8. PRO1293 showed approximately 1.71 ΔCt unit which corresponds to $2^{1.71}$- fold amplification or 3.272-fold amplification in primary lung tumor (HF-000840), and approximately 1.13-2.33 ΔCt units which corresponds to $2^{1.13}$ -$2^{2.33}$- fold amplification or 2.189 fold to 5.028-fold amplification in colon tumors (HF-000539 and HF-000795). (See Table 8 and page 503, lines 4-11 of the specification).

It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis.

In support, Applicants submit a Declaration by Dr. Audrey Goddard with this response and particularly draw the Examiner's attention to page 3 of the declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for

monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

The attached Declaration by Audrey Goddard clearly establishes that the TaqMan real-time PCR method described in Example 143 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO1293 is a useful target for therapeutic intervention in lung and colon tumors.

Secondly, regarding the Examiner's point that "the claimed invention is not supported by either a substantially asserted utility or a well established utility," Applicants submit, as discussed below, that the Examiner has not established a *prima facie* case for lack of utility for PRO1293 polypeptide.

Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re* Langer, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re* Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.

Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the applicant. The issue will then be decided on the totality of evidence.

A prima facie case of lack of utility has not been established

The Examiner bases the conclusion of lack of utility on a quote from Pennica *et al.* According to the quoted statement, "WISP-1 gene amplification in human colon tumors showed a correlation between DNA amplification and over-expression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient." From this, the Examiner correctly concludes that increased copy number does not *necessarily* result in increased polypeptide expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. The Examiner has not shown whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, a correlation between DNA amplification and over-expression of polypeptide **was observed** in the case of WISP-1.

Even if a prima facie case of lack of utility had been established, it should be withdrawn on consideration of the totality of evidence

Even if one assumes arguendo that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and substantial utility. In support, Applicants submit a declaration by Dr. Avi Ashkenazi, Ph.D., an expert in the field of biology and an inventor of the present application. Applicants particularly draw the Examiner's attention to page 2 of the declaration which explains that,

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also the patient need not be exposed to the side effects associated with such agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. (Oathology Associates Medical Laboratores, August (1999), copy enclosed). The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

Applicants also submit that there are numerous articles which show that generally, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. For example, Orntoft *et al.* (*Mol. and Cell. Proteomics*, 2002, Vol.1, pages 37-45, copy enclosed) studied transcript levels of 5600 genes in malignant bladder cancers

many of which were linked to the gain or loss of chromosomal material using an array-based method. Ornoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (*Cancer Res.*, 2002, Vol. 62, pages 6240-45, copy enclosed) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (See page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.*, (*PNAS*, 2002, Vol. 99, pages 12963-12968, copy enclosed) who studied a series of primary human breast tumors and showed that "62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

Finally, enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared

the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1293 gene, that the PRO1293 polypeptide is concomitantly over-expressed. Hence the PRO1293 polypeptides have utility in the diagnosis of cancer.

In view of the above, Applicants request the Examiner to reconsider and withdraw the rejection of Claims 28-36 and 38-40 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

Claim Rejection Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 28-40 are rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility ..., one skilled in the art would not know how to use the claimed invention".

Applicants respectfully disagree and traverse the rejection.

Applicants respectfully disagree and traverse the rejection.

Applicants submit that the cancellation of Claim 37 renders the rejection of this claim moot.

In response to the rejection under 35 U.S.C. §101, Applicants have shown above that the specification discloses a substantial, specific and credible utility for the PRO1293 polypeptide. Further, without acquiescing to the Examiner's position in the current rejections, and without prejudice to further prosecution of the subject-matter in one or more continuation or divisional applications, Claims 28-32 (and, as a consequence, those claims dependent from the same) have been amended to recite " wherein the nucleic acid encoding the polypeptide is amplified in lung or colon tumors." Since the claimed genus is now characterized by a combination of structural and functional features, any person of skill would know how to make and use the invention without undue experimentation based on the general knowledge in the art at the time the invention was made. As the M.P.E.P. states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" *In re Certain Limited-charge cell Culture Microcarriers, 221 USPQ 1165, 1174* (Int'l Trade Comm'n 1983), *aff'. sub nom., Massachusetts Institute of Technology v A.B. Fortia,* 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985) M.P.E.P. 2164.01.

In view of the discussions above regarding the utility of the polypeptides, Applicants submit that Claims 28-36 and 38-40 satisfy the enablement requirement because one skilled in the art would know how to make and use the claimed polypeptides. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejection Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 28-32 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of sufficient written description. The Examiner alleges that the claims are directed to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity to the polypeptide of SEQ ID NO: 77, or the polypeptide of SEQ ID NO: 77 lacking its associated signal peptide, but the specification does not teach functional or structural characteristics of all the claimed

polypeptides. Thus, the Examiner notes that in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Without acquiescing to the Examiner's position in the current rejections, and without prejudice to further prosecution of the subject-matter in one or more continuation or divisional applications, Claims 28-32 (and, as a consequence, those claims dependent from the same) have been amended to recite "wherein the nucleic acid encoding the polypeptide is amplified in lung or colon tumors." Furthermore, the term "lacking its associated signal peptide" is no longer present in Claims 28-32 (and, as a consequence, those claims dependent from the same). This biological activity, coupled with a well defined, and relatively high degree of sequence identity are believed to sufficiently define the claimed genus, such that one skilled in the art would readily recognize that the Applicants were in the possession of the invention claimed at the effective filing date of this application. Hence, the present rejection should be withdrawn.

Claim Rejections - 35 U.S.C. §102

The examiner noted that the priority of the instant application is set at December 6, 2001. As discussed above, Applicants respectfully submit that the effective filing date of the present application is October 29, 1999.

Claims 28-40 are rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Bostein *et al.*, WO 2000053751, published on September 14, 2000. As discussed above, Applicants are entitled to an effective filing date of October 29, 1999, and hence, Bostein *et al.* is not prior art under 102(a) since its filing date is after the effective priority date of this application. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claims 28-40 are rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Baker *et al.*, WO 200012708, published on March 9, 2000. As discussed above, Applicants are entitled to an effective filing date of October 29, 1999, and hence, Baker *et al.* is not prior art under 102(a) since its filing date is after the effective priority date of this application.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C3**).

Respectfully submitted,

Date: September 9, 2004

By: _____
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